THE EVOLUTION OF OUR PRESENT KNOWLEDGE OF HYPERSENSITIVENESS*

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IN the light of the fact that the hypersensitive reactions are often of startling intensity and the onset of symptoms most sudden, it is not to be wondered at that the noticeable contrast between the reaction of the idiosyncratic and other persons against one and the same agent has commanded attention from time immemorial. The condition of hypersensitiveness per se was recognized at a very early period.[1] Greek and Roman authors described the phenomenon by the term "idiosynkrisie" which is used today. Galen employed the term "idiopathy." The thought of the time, as is evidenced in this terminology, centered about attempts to gain an insight into constitutional deviations of the idiosyncratic, emphasis apparently being placed upon individual disposition rather than upon environmental factors. Though the dawn of the twentieth century ushers in the true beginnings of our present knowledge of allergy, we might pause a moment to reflect that no new discovery is ever so entirely original that it does not have its roots in the past.

Elliotson,[2] in London, in 1831, was the first to seek an etiologic factor in the pollens of the blossoming grasses. This work, taken up by Blackley[3] in Manchester in 1873, was greatly extended by the latter's use of the "skin and mucous membrane tests," inoculation of flower dust into scarified skin, and inhalation of pollen. Blackley's publication stated that a disease described by John Bostock[4] in 1819 as a "periodical affection of eyes and chest" and later as "catarrhus aestivus" was viewed etiologically as a "pollen catarrh" and that this was related to those idiosyncrasies which were known even in Galen's time as "rose cold." There was little opposition to the "pollen theory." Dunbar,[5] in 1903, confirmed the findings of Elliotson and Blackley and corrected the impression of the English authors on two important points, namely, that hay fever sufferers were hypersensitive during the non-pollinating sea-

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son, and, secondly, that there was a relative specificity of pollen idiosyncrasy.

Some of the early observations are of interest in showing how inevitable the discovery of anaphylaxis was with the introduction of the experimental method. Scattered communications appeared which were concerned with increased reactions produced by repeated injections of foreign materials. In 1890, Koch[6] first clearly demonstrated the phenomenon of hypersensitivity to a specific substance in his experiments with tuberculin. We glean from Morgenroth[7] that in 1839 Magendie observed that white rabbits easily tolerated a first injection of albumin but that some days later they could not tolerate the injection of a similar dose. Flexner[8] (1894), too, observed that rabbits, surviving a first injection of dog serum without a symptom, some days or weeks later died when given an equal or even smaller dose. Behring,[9] in 1893, studying the effects of diphtheria toxin on guinea pigs, showed that these animals, once injected with the toxin, became in certain cases intensely sensitive to it; but he did not consider the phenomenon either general among the injected animals or common to all poisons. Studying immunity particularly, he considered hypersensitivity a "paradoxical reaction." He made the statement that horses, under immunization, possessing large amounts of antitoxin in their blood showed hypersensitiveness to the toxin. These animals in all probability did not develop symptoms referable to the specific action of the toxin injected, for toxin is never injected in a pure state. The symptoms were, therefore, most probably due to the associated materials in the media. In 1894, Arloing and Courmont[10] noted that successive injections of donkey serum produced toxic effects in man. Courmont,[10] in 1900, noted that on inoculating guinea pigs with successive and very weak doses of the effusion of tuberculous pleurisy, the animals died before receiving a quarter of the total dose they originally took as a single injection, without ill effect.

These investigators did not realize that they had stumbled upon a phenomenon not heretofore described or named. It was Charles Richet,[11] the French physiologist, who in 1902 recognized the novelty of the phenomenon so many others had chanced upon yet did not comprehend, and it was he who correlated his observations and followed them out to their logical conclusions.

Yet, it is interesting to recall that in 1898 Richet[12] himself com-

pletely missed his opportunity while he and Héricourt were studying the effects of eel serum on dogs. He noticed that the second injection, and the third even more markedly, made them sick and waste away. Richet admitted later that he did not understand the significance of this result and contented himself with supposing there was increased sensitivity without attempting to analyze the phenomenon. Opportunity knocked at his door once again, which happens more often than we are ready to believe. As Richet[13] so aptly remarked in his book, "The Natural History of a Savant," one can work a life time on a problem and develop nothing of fundamental importance, yet occasionally one may chance upon a great discovery after but a short period of work. So it was with his discovery of anaphylaxis. He chanced upon a phenomenon in biology which bids fair to take its place amongst the great discoveries and for which he received the Nobel Prize. It has opened the door to the understanding of a host of conditions which afflict mankind. In this sense then we can say that the dawn of the 20th century is the true beginning of our basic knowledge of hypersensitiveness.

Richet's[14] discovery was made in the course of his study of toxins with which he attempted to immunize dogs. Animals which withstood the lethal dose were later again injected with the same toxin. It was these reinjection experiments which drew his attention to the peculiar phenomenon to which he gave the name "anaphylaxis." The experiment which led to his discovery will be briefly quoted here.

> "During a cruise on Prince Albert of Monaco's yacht, the Prince and G. Richard suggested to P. Portier and myself a study of the toxic properties of the Physalia found in the South Seas. On board the Prince's yacht experiments were carried out, proving that an aqueous glycerin extract of the filaments of Physalia is extremely toxic to ducks and rabbits. On returning to France, I could not obtain any Physalia and decided to study comparatively the tentacles of actinaria, which resembles physalia in certain respects and are easily procurable. Owing to the kindness of Y. Delage, I was able to obtain a large quantity; the tentacles cut close to the body were placed in glycerin and thus we had in Paris several liters of an intensely toxic fluid, the glycerin dissolving and extracting the active principle. While endeavoring to determine its toxic dose, we soon discovered that some days must elapse before fixing it, for several dogs did not die until the fourth or fifth day or even later after administration. We kept those which had been given a dose insufficient to kill, in order to carry out a second investigation upon them when they had completely recovered.
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> "At this point, an unforeseen event occurred. The dogs which had recovered were intensely sensitive and died a few minutes after the administration of subsequent small doses.
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> "The most typical experiment, that in which the result was indisputable, was carried out on a particularly healthy dog named "Neptune." He

> was given at first 0.1 c.c. of the glycerin extract without becoming ill; twenty-two days later, as he was in perfect health, I gave a second injection of the same amount. In a few seconds, he was extremely ill; breathing became difficult, and he was panting. He could scarcely drag himself along, lay on his side, was seized with diarrhea, vomited blood, sensibility diminished, and he died in twenty-five minutes."

It has always been a source of wonder to me that Richet should have discovered anaphylaxis with a substance that was highly toxic and that this discovery should have been consummated in the dog, for Weil[15] and others have since shown that anaphylaxis is difficult to induce in the dog.

Richet's observation was first attributed to toxin accumulation, and yet, he stated that the symptoms of this reaction differed greatly from primary intoxication studies. His systematic investigations revealed that the described phenomenon is produced at least 2 or 3 weeks after the first injection, which definitely excluded the cumulative concept. Richet determined that the first toxin injection in his animals not only caused no antitoxic immunity but rather that it produced an increase in the toxin sensitivity which was manifested after the course of a certain incubation period. The first toxin injection did not act "prophylactically" in these animals, but in contrast, as Richet termed it, "anaphylactically." The first toxin injection transformed the animals into a state of "anaphylaxis" (without protection).

On the heels of Richet's discovery came Arthus[16] (1903) who demonstrated that a non-toxic protein may also produce hypersensitiveness. According to the pioneer observations of Arthus, rabbits react neither to subcutaneous, intraperitoneal nor intravenous primary injections of horse serum. On the other hand, when rabbits previously sensitized to horse serum are reinjected intravenously, very severe symptoms appear almost immediately which may lead to anaphylactic death in two to four minutes. If the horse serum is injected subcutaneously at six-day intervals, resorption of the serum takes place after the first three of such injections. However, after the fourth injection, infiltration appears which finally develops into necrosis, sequestration and abscess formation. This, Arthus described as local anaphylaxis, known today as the "Arthus Phenomenon." The use of the terms "local" and "general" anaphylaxis leave no doubt that Arthus identified his observations with those of Richet.

His experiments were successful not only with horse serum but also

with cow's milk. However, rabbits sensitized with the one substance were unharmed by the other, thereby demonstrating the specificity of anaphylaxis. Since Richet and Arthus resorted to such varied stuffs as the toxic actino congestin and nontoxic cow's milk and horse serum, it became evident that anaphylaxis could be produced with substances which are very different from each other in chemical properties and in physiological action.

Many substances and various animal species were subsequently used to demonstrate anaphylaxis and yet, not until the guinea pig was utilized were really decisive results obtained. The guinea pig became the experimental animal of choice in this field after Theobald Smith[17] made the following observations (1905). In the course of his work on the standardization of diphtheria antitoxin, Smith noted that guinea pigs, which several weeks before had received a dose of diphtheria toxin and antitoxic horse serum, showed severe symptoms or died immediately after reinjection with several cc. of normal horse serum. Ulrich Friedemann[18] who was working in Ehrlich's laboratory informs me that although such reactions in guinea pigs to repeated injections had been observed for some time, no particular interest was evoked until Ehrlich returned to his laboratory in Germany after a visit to Smith in America. He suggested to Otto,[19] one of his assistants, that he work on this problem. Otto called it the "Theobald Smith Phenomenon." One is tempted to feel that Otto, the German, preferred to credit an American rather than the Frenchmen, Richet and Arthus, with this fundamental discovery.

Because of the ease with which this phenomenon could be produced in the guinea pig, the work stimulated by Smith awakened a tremendous and widespread interest in the subject of hypersensitiveness. The same conclusions as Smith's were drawn by Rosenau and Anderson[20] in America, and in rapid succession by many others.

The first recorded foreign serum injection into man, that of lamb blood, was given in 1667, by Deins.[21] No ill effects were ascribed to this introduction of foreign serum, until the beginning of the 19th century, when the intravenous introduction of lamb blood was discovered to be accompanied by grave danger, resulting in high fever, emboli, bleeding and hemoglobinuria. The cause for these reactions was first explained by Landois[22] and Ponfick, in the latter part of the 19th century, but their explanations were concerned with incompatibility of blood cells. At about this time, urticarial eruptions were observed to occur several

days after transfusions. Dallera[23] described a case of a girl with "hysterical mania" whose whole body was covered with urticaria ten days after transfusion. Other reports soon followed. Because of the ill effects of lamb blood transfusions, animal blood transfusions were almost completely abandoned. Dominicis,[24] in 1895, tried to revive their use. Milk transfusions were also attempted but soon disappeared from medical annals because they were found to be useless and dangerous.

Since Pasteur's discovery, in the middle of the 19th century, that infectious agents are the cause of certain diseases, attempts have been made to aid the body in specifically neutralizing invading bacteria and accelerating the mechanism of immunity. This has given rise to the use of antitoxic and antibacterial sera obtained from other animal species. In 1894, the treatment of diphtheria with antitoxic horse serum had been introduced by Behring.

Lublinski[25] was probably the first to publish a case of exanthem after the injection of a therapeutic serum. An eight-year old girl, on the second and third days of her illness, received injections of 0.3 cc. Behring's diphtheria antitoxin. On the fifth day of her illness there was a red area around the site of the injection. Nine days after the last injection she developed high fever, multiple and painful joint swellings with a widespread multiform erythema and a macular eruption. This severe syndrome lasted for four days. With the recession of the exanthem the joint pains and swelling diminished.

Experimentally Johannessen[26] gave proof that the active agent in the production of these sequelae was not inherent in the antitoxic content, but something in the horse serum itself since the same symptoms were produced in non-diphtheritic persons with normal horse serum. A large number of publications appeared in the literature with respect to this syndrome which was called "serum exanthem" because of the cardinal symptom of skin eruption.

But no careful analysis of this condition was made until von Pirquet and Schick[27] published their classic monograph in 1905, "Serum Krankheit." The new term, serum sickness, included all the other symptoms besides the exanthem. They explained the clinical manifestations in the following way. Foreign serum acts on man as an antigen. Antibody, which develops in the organism as a result of the antigen, upon union with the horse serum produces the symptoms. Serum sickness is therefore an in-vivo, antigen-antibody reaction. The incubation period de-

pends upon the completion of the appearance of the antibodies and the presence of horse serum still remaining in the blood.

An important step in linking up the mechanism of serum sickness with allergy was the work of Hamburger and Moro[28] who, in 1903, demonstrated that precipitins resulted after the introduction of foreign serum.

Little notice might have been taken of the experiments of Richet and Arthus on anaphylaxis in its application to man had not von Pirquet and Schick found that *reinjection* of serum at some later date results in immediate and accelerated reactions, which phenomenon they called "allergy"—altered reaction. Charles Richet did not easily forgive von Pirquet for coining the term allergy, for, he argued, is not anaphylaxis sufficient to describe the phenomenon in both animal and man? One can appreciate his feelings, but usage and euphony have given to allergy the greater popularity. Furthermore, von Pirquet[29] used the term allergy in a broader sense than Richet, who considered anaphylaxis only from the standpoint of hypersensitiveness to foreign proteins. von Pirquet included all reactions to foreign proteins and infectious agents and laid the groundwork for our understanding of the relationship between allergy and immunity. One is in the best of company, however, whether one adheres to the term allergy, or prefers anaphylaxis.

The immediate character of the anaphylactic reaction described by Richet and Arthus would therefore in the light of von Pirquet and Schick's work be explained on the basis of the presence of previously formed antibodies. This conception of serum sickness and anaphylaxis as vital antigen-antibody reactions has served to elucidate many varied phenomena which at first appeared widely divergent but were later shown to depend on this basic concept. In the short period between 1902 and 1910 practically all the principles of hypersensitiveness were laid down.

One cannot deny that many diseases have been controlled through the use of antisera, but in their wake have come not only the relatively harmless serum disease, but the more serious serum allergy and anaphylaxis. Though the reaction to the invasion of foreign materials is purely a physiological one, the tempo of reaction is invariably accelerated. A knowledge of these reactions should lead to a more intelligent management of disturbed conditions that result paradoxically from a beneficent curative procedure.

For practical clinical purposes—so far as danger to life is concerned—

primary contact with foreign substances should always be carefully distinguished from secondary or repeated contacts. But, whether primary serum sickness or serum allergy are under consideration the basic similarity of their mechanisms must be kept in mind. Thus after primary contact with a foreign substance nothing transpires until an incubation period elapses, during which time specific antibodies are formed. When this supervenes, the foreign substance still present in the body reacts with the newly formed antibodies and the signs and symptoms of serum sickness become manifest in the different tissues. On the other hand, by allergy is meant the reaction which ensues when antibodies are present in the tissues as a result of previous contacts and when the specific antigen again enters the body a reaction takes place immediately or shortly thereafter without a prolonged incubation period.

Whether the invading foreign substance is a serum, food, inhalant, drug, or hormonal extract, the body response in each instance is fundamentally the same, differing only with respect to the tissues directly involved. From all of this, it must be apparent that the organism is so constructed that it continually impedes the invasion into the circulation of materials that cannot be utilized by the body economy. There are periods, however, when the organism fails to prevent the entrance into the body of inimical agents, such as bacteria, viruses, chemicals, toxins, and foreign proteins. When such invasions of foreign agents do occur, the organism may become either (1) damaged or destroyed, (2) allergic, or (3) immune.

There is a growing impression that allergy inevitably precedes a state of immunity.[30] Immunity, however, is not static, and an individual immune at one time may again become allergic. These changing conditions in the same individual depend largely on whether the antibodies are anchored to cells alone—the allergic state, or whether the antibodies are present in greater abundance in the circulation, neutralizing the antigen before it reaches the antibody containing cells—the immune state.

Another factor of great importance is that when the invasive substance is a viable antigen, such as a bacterium, it multiplies in the body and thus complicates the situation by destroying tissues through the production of endotoxins and exotoxins. On the other hand when the substance is not viable—serums, foods, pollens, etc.—and therefore nonmultipliable, no destructive lesions result, and the reaction is dependent entirely on the actual amount of antigen which invades the body at that particular time.

The evolution of our present concept of allergy is thus unfolded. But a small part of the story has been told, as may well be imagined. Some may question my omission of such developments as the anaphylotoxin theory, the protein cleavage concept, atopy, the histamine basis for allergy, the Schultz-Dale phenomenon, Otto's and others' work on passive anaphylaxis, the heterophile studies by Friedemann and others, the work emanating from the Prausnitz-Küstner phenomenon, and our own work on congenital hypersensitiveness and experimental asthma. My main purpose, however, was to show that this subject—whether we speak of it as hypersensitiveness, allergy, anaphylaxis, atopy or any other term that has been devised—is not young. The course of its growth has not been direct, and amongst the deviations have been the developments above named. Each has undoubtedly added something to our general knowledge, but to them we must assign a minor role.

As I see it, the major role in this ubiquitous drama is played by the antigen-antibody tissue reaction. We may sum it up simply as follows. A substance, foreign to the body economy, which in and of itself is harmless when entering the body for the first time, may produce a disturbance upon subsequent invasion. This is due to an interaction between the specific antigen and its related antibody which has been elaborated and become fixed to the smooth muscle cells of some organ or organs in the interim between the primary and secondary invasions of the antigen. The union produces cellular irritation with concomitant spasm and probable physico-chemical reactions of the sensitized tissue.

The type of syndrome produced depends upon the characteristics of the tissue irritated. Such a unitarian concept is supported by a wealth of sound observation. It enables us to conceive how such varied syndromes as serum sickness, eczema, hay fever, asthma, disturbances of the gastrointestinal tract, central nervous system, the liver and other organs, are all manifestations of the one phenomenon—a simple union of antigen and antibody with differing chemical, physiological and pathological secondary effects.

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